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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,991	04/13/2006	Lital Alfonta	54000711US	2082

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EXAMINER

GEBREYESUS, KAGNEW H

ART UNIT	PAPER NUMBER
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1656

MAIL DATE	DELIVERY MODE
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02/07/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/575,991

Applicant(s)

ALFONTA ET AL.

Examiner

Kagnew H. Gebreyesus Ph.D

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31, 33-36, 38-39 and 41-47 is/are pending in the application.
- 4a) Of the above claim(s) 1-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31, 33-36, 38, 39 and 41-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 4/13/06 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response to the notice of abandonment mailed on October 9, 2007 is acknowledged. It appears that Applicants have mailed a reply on September 26, 2007 in response to the Office Action mailed on March 26, 2006. Furthermore Applicant's request on October 19, 2007 to withdraw holding of abandonment is granted. The notice of abandonment mailed on October 9, 2007 is withdrawn. Claims 1-31, 33-36, 38-39, 41-44 and new claims 45-47 are pending. Claims 1-30 are withdrawn as being part of non-elected subject matter. Claims 31, 35, 36, 38, 38, 42 and 43 are amended. Claims 32, 37 and 40 are cancelled. Claims 31, 33-36, 38, 39, 41-47 are present for examination

Withdrawn - Claim Objections

The objection to claim 40 is moot since the claim has been canceled.

Maintained - Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 remains rejected for the recitation "at least 75% identical to that of a wild type therapeutic protein, a diagnostic protein, an industrial enzyme or a portion thereof".

Applicant's argument has been considered carefully. While it is acknowledged that the specification provides a non-exhaustive list of therapeutic proteins, diagnostic protein, and industrial enzymes, it is not clear if a claimed protein exhibiting 75% identity to a wild type of therapeutic protein, diagnostic protein, and industrial enzyme also retains functional activity. If the claimed proteins with 75% identity are inactive because of a 25% variation in sequence, it is not clear what the utility of such proteins would be. If on the other hand the claimed proteins with 75% identity have activity, the limitation "75% identity" is not further limiting because such proteins and others with lower similarity would also be within the limitation of a therapeutic, a diagnostic protein, or an industrial enzyme. Therefore clarification will be required..

For examination purposes these proteins will be encompassed as active therapeutic, diagnostic protein, or industrial enzymes.

Claim 42 is objected to for the recitation: "improved oxidation". This rejection is withdrawn following amendment to the claim.

Withdrawn -Claim Rejections - 35 USC § 102

Claims 31, 33, 34, 39-44 as applied to claims 31, 33, 34, 41-47 were rejected under 35 U.S.C. 102(a) as being anticipated by Alfonta et al. (Site Specific Incorporation of a Redox-Active Amino Acid into Proteins. 2003. Journal of American Chemical Society. 2003, 125, 14662-14663). This rejection is withdrawn because Applicant's argument regarding priority is found persuasive.

Claims 31, 33, 39, 41-44 as applied to claims 31, 33-36, 38, 39, 41-47 rejected under 35 U.S.C. 102(b) as being anticipated by Rodriguez et al. (The Reciprocal Exclusion by L-Dopa (3,4-hydroxy-L-phenylalanine and L-Tyrosine of their incorporation as Single Units into a Soluble Rat Brain Protein, Biochemistry Journal (1975) 149, 115-121). This rejection is withdrawn following Applicants claim amendment and argument.

Withdrawn - Claim Rejections - 35 USC § 102

Claims 31, 33-44 as applied to claims 31, 33-36, 38, 39, 41-44 were rejected under 35 U.S.C. 102(e) as being anticipated by Schultz et al (US 7, 045,337 B2) as evidenced by Rodriguez et al. (The Reciprocal Exclusion by L-Dopa (3, 4-hydroxy-L-phenylalanine and L-Tyrosine of their incorporation as Single Units into a Soluble Rat Brain Protein, Biochemistry Journal (1975) 149, 115-121). However the following rejection applies to the amended claims and dependent claims thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31, 33-36, 38, 39, 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al (US 7, 045,337 B2) in view of Rodriguez et al.

Applicants teach how to screen for an ORS/OtRNA pair that can be used for incorporating specific unnatural amino acids into a protein. The ORS/OtRNA pair identified in the screening method is then used to produce a protein comprising the specified unnatural amino acid. As a working example, Applicants disclose a myoglobin protein comprising a single redox-active amino acid, namely 3, 4-dihydroxy-L-phenylalanine (DHP or L-DOPA).

Based on the above teaching which serves as proof of principle for incorporating a redox-amino acid in a protein, Applicants claim a protein comprising at least two redox-active unnatural amino acids selected from 3, 4-dihydroxy-L-phenylalanine, a 3, 4, 5-trihydroxy-L-phenylalanine, a 3-nitro-tyrosine, a 4-nitro-phenylalanine and a 3-thiol-tyrosine in claims 31 and dependent claims 33-36, 38, 39 and 41-44.

In line with the above teachings, Schultz et al's (US 2003/0082575 A1) disclose an identical screening method that identifies a specific ORS that preferentially aminoacylates an O-tRNA with a specific unnatural amino acid which is incorporated into a protein. Furthermore similar to Applicant's disclosure above, Schultz et al provide an example of a myoglobin protein comprising an unnatural amino acid.

Furthermore Schultz et al teach compositions comprising a protein, wherein the protein comprises at least two unnatural amino acids (see claims 33).

Schultz et al do not specifically exemplify a myoglobin protein comprising at least two redox-active amino acids in a protein. However it would have been obvious for a person of ordinary skill in the art to incorporate one, two or more unnatural amino acids including any type of redox-active unnatural amino acids such as those disclosed in

paragraphs [0045], [0046], figures 17 and 29 which specifically teaches the redox-active amino acid 3, 4-dihydroxy-L-phenylalanine (DHP) into any protein and [0028, 0149] that teach any redox-active amino acids).

Claim 34 in the instant application is obvious because a protein comprising an unnatural amino acid that can optionally be employed for therapeutic use in combination with a suitable pharmaceutical carrier is disclosed in paragraph [0246] of Schultz et al.

Claims 35, 36, 38 and 43 are obvious over Schultz et al paragraph [0173] because Schultz et al teach that in a protein composition where more than one unnatural amino acids are incorporated, the unnatural amino acids can be identical or different (e.g., the protein can include two or more different types of unnatural amino acids, or can include two or more different sites having unnatural amino acids, or both see paragraph paragraph [0173]).

Claim 39 drawn to a myoglobin protein comprising at least two redox-active amino acids is obvious because Schultz's teach a myoglobin protein comprising an unnatural amino acid. Furthermore claim 25 in Schultz et al teaches that the protein composition can have two or more unnatural amino acids. Such unnatural amino acid can be any unnatural amino acid including any redox-active unnatural amino acid.

Furthermore the desirable properties of redox active unnatural amino acids in claims 41, 42 and 44 are also obvious because paragraph [0153] of Schultz et al. (US 7, 045,337 B2) teaches specific desirable properties of unnatural amino acids incorporated into proteins. Schultz et al states;

"[0153] Typically, the unnatural amino acids of the invention are selected or designed to provide additional characteristics unavailable in the twenty natural amino acids. For example, unnatural amino acid are optionally designed or selected to modify the biological properties of a protein, e.g., into which they are incorporated. For example, the following properties are optionally modified by inclusion of an unnatural amino acid into a protein: toxicity, bio-distribution, solubility, stability, e.g., thermal, hydrolytic, oxidative, resistance to enzymatic degradation, and the like, facility of purification and processing, structural properties, spectroscopic properties, chemical and/or photochemical properties, catalytic activity, redox potential, half-life, ability to react with other molecules, e.g., covalently or non-covalently, and the like".

The embodiments in claims 41 and 42 drawn to a protein capable of undergoing oxidation or improved oxidation, is regarded as an inherent property of any redox-active containing protein.

Thus one of ordinary skill in the art would have a reasonable expectation of success that a redox-active amino acid incorporated in a growing polypeptide will have the ability to undergo oxidation or improve oxidation because the method of incorporating an unnatural amino acid is taught by Schultz et al in view of Rodriguez et al who confirm that the redox-active unnatural amino acid, 3, 4-hydroxy-L-phenylalanine can be incorporated into a protein in such a way that it excludes or competes with the incorporation of L-tyrosine.

One of ordinary skill in the art would have been motivated to produce proteins comprising unnatural amino acids such as redox-active amino acids because unnatural amino acids provide novel functionalities useful in biological processes as stated above.

Therefore claims 31, 33-36, 38, 39, 41-44 are obvious over Schultz et al as evidenced by Rodriguez et al.

New grounds of Objection and Rejections based on amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 45-47 are drawn to a composition comprising any protein with two or more redox-active amino acids, at least one orthogonal t-RNA (O-tRNA), at least one orthogonal tRNA synthetase (ORS) wherein the O-RS preferentially aminoacylates said OtRNA and any nucleic acid with at least two selector codons that encodes a protein of interest (claim 45). Furthermore claim 47 is drawn to an ORS that has 50% efficiency as compared to an ORS of SEQ ID NO: 1 or an ORS a conservative variant of SEQ ID NO: 1 (claim 46). However the specification only provides a description of a composition comprising the ORS of SEQ ID NO: 1 that aminoacylates a corresponding O-tRNA with the specific unnatural amino acid, 3,4-dihydroxy-L-phenylalanine (DHP) and wherein said unnatural amino acid is incorporated into a protein of interest.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. " For claims drawn to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses the ORS of SEQ ID NO: 1 that aminoacylates the corresponding O-tRNA with 3, 4-dihydroxy-L-phenylalanine (DHP) and the myoglobin gene with a single selector codon and the myoglobin protein comprising DHP. Thus the above composition is not representative for the genus of proteins, ORS, OtRNA and nucleic acids encompassed in the claims, because, to fully describe a genus of genetic material, which is a chemical compound Applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics when coupled with a known or disclosed correlation between function

and structure, or a combination thereof.

Thus the specification fails to describe a representative number of compositions by any identifying characteristics or properties other than the functionality of being a protein comprising two or more redox active amino acids, ORS, and OtRNA and a nucleic acid with at least two selector codons. Furthermore the composition comprises an ORS variant of SEQ ID NO: 1 or an ORS that has an efficiency of 50% compared to the efficiency of SEQ ID NO: 1.

While MPEP § 2163 acknowledges that in certain situations “one species adequately supports a genus”, it also acknowledges that “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.” In the instant case the recited compositions encompasses species widely variant with respect to the structures, which include any protein from any source comprising two or more redox active amino acids, any ORS with 50% or more efficiency observed relative to SEQ ID NO: 1 and conservative variants relative to SEQ ID NO: 1.

As such, the only structure described in the specification is the ORS of SEQ ID NO: 1 that aminoacylates the corresponding O-tRNA of SEQ ID NO: 2 with a single redox-active amino acid (DHP). The specification does not provide a description of any other ORS/O-tRNA pair molecules that can be used to incorporate any other unnatural amino acid. Claim 44 is drawn to a composition comprising a redox-active amino acid having catalytic activity. However the specification does not describe the structure of

any a redox-catalyst unnatural amino acid wherein said unnatural amino acid can be incorporated into a protein using any specific ORS/OtRNA pair.

However this description is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus encompassed in claims 45-47 because the specification fails to identify the common characteristics of the claimed molecules, e.g. structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination thereof. In the instant case all of the recited genus of molecules are claimed by function without a known correlation of structure/function.

Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Conclusion:

Claims no claims are allowed.

Relevant reference(s): A New Redox Cofactor in Eukaryotic Enzymes: 6-Hydroxydopa at the Active Site of Bovine Serum Amine Oxidase. 1990. Janes et al. Science. Vol. 248, No. 4958 (May, 1990), pp. 981-987.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

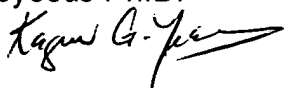
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagne H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kagne H Gebreyesus Ph.D.
Examiner
Art Unit 1656



/Jon P. Weber/
Jon P. Weber
Supervisory Patent Examiner,